REMARKS

As a preliminary matter, please note the Request for Continued Examination (RCE) submitted herewith.

Claims 2, 7-9, 12-32, 44-45, 56, 49-51, 56-57, 63-81, 88-97, 101, 103-108, 118-122, 124, and 130-131 are currently pending in the application. Claims 58-62 will be rejoined if the claims are found to be allowable.

In the office action, the Examiner rejected claims 2, 7-9, 12-32, 44-45, 49-51, 56, 63-81, 88-97, 101, 103-108, 118-122, 124, and 130-131 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (4,765,989) in view of Stevens et al (5,897,874). Wong et al. is directed toward sustained delivery of the drug by extrusion of the drug layer through an opening in a coating surrounding the core of an osmotic tablet. In contrast, Stevens et al. is directed toward a two-part capsule that separates to provide release of substantially all of the drug following a delay. The examiner took the position that Wong et al. teaches an osmotic dosage form having all of the claim limitations of claim 2 with the exception of a highly swelling water swellable composition, and that Stevens et al. discloses certain highly swelling materials for use in connection with water swellable capsules. The examiner concluded that it would have been obvious to a person of ordinary skill in the art to combine the osmotic dosage form of Wong et al. with the highly swelling materials used in the delayed release capsules of Stevens et al.

The rejection is traversed on the basis that it would not have been obvious to make the combination suggested by the Examiner. Claim 2 requires a controlled release dosage form with a drug-containing composition and a water-swellable composition. The water-swellable composition comprises a swelling agent and a tabletting aid. The swelling ratio for the water-swellable composition is ≥ 3.5, and the tablet strength is ≥ 3 Kp/cm^2. Thus, the claim requires a water-swellable composition that provides both a high degree of swelling and good strength. As described in the application, one of the problems that results from using highly swelling water swellable materials is that such highly swelling materials are difficult to compress to a hardness suitable for use. Page 30, lines

31-33 of the application. The inventors solved the problem by combining swelling agents having a high degree of swelling with a tableting aid to achieve both good release and good tablet strength. Page 30, line 34 – Page 31, line 5. Thus the invention relates specifically to compressed tablets.

Wong et al. disclose an osmotic device comprising a drug-containing composition and a water-swellable composition. Wong et al. teach that a variety of materials may be used for the osmopolymer or hydrogel in the water swellable composition. See Col., 15 line 63 – Col. 16, line 46. In the examples, Wong et al. disclose a water swellable composition comprising poly(ethylene)oxide having a molecular weight of 5,000,000 or 6,000,000 and sodium chloride. As demonstrated in the Declaration of Scott McCray submitted with Applicants' prior response, this type of water swellable composition does not meet the claim limitation that the water swellable composition have a swelling ratio of at least 3.5 as required by the claim. There is no discussion in Wong et al. regarding the desirability of using highly swelling water swellable materials, the difficulty in compressing tablets containing such materials to a hardness suitable for use, or that the water swellabe composition should contain a tableting aid.

Stevens et al. do not disclose an osmotic tablet. Instead, Stevens et al. disclose a delivery device in the form of a capsule comprising a male hydrogel plug engaged in the neck of a female body. The male hollow body contains a water swellable material that causes the female neck to become disengaged. The delivery device of Stevens et al. thus provides a pulsed or delayed release, in which the active agent is rapidly released from the device after an initial delay of 2 – 10 hours. Some of the expandable excipients disclosed in Stevens et al. are highly swelling materials, such as sodium starch glycolate, tradename Explotab, and carboxymethyl cellulose, tradename Ac-Di-Sol.

In Stevens et al., there is no recognition of the need to achieve good tablet strength, since Stevens et al. disclose the use of a capsule. It is known by persons skilled in the art that compared with tablets, powders for filling capsules require the minimum of formulation efforts. See Remington: The Science and Practice of Pharmacy, 19th Ed. (1995) Vol. II at page 1643 (attached). There is

no recognition in Stevens et al. that the water swellable composition must be formulated to combine both a swelling agent with a high degree of swelling and a tableting aid. In contrast, Stevens et al. states that the expandible excipient may include "minor amounts of formulating excipients" for the purpose of wetting, improving flow properties, or wicking. Col. 4, lines 32-43. There is no discussion of including excipients to improve tableting. In fact, Stevens et al. teach away from the use of compressed tablets. According to Stevens et al., the hardness of the solid slug used in the capsule may be less than for conventional tablets. Col. 5, lines 3-4. This slug is filled into "an impermeable hollow female body", and a minimum tablet hardness is not required.

Many of the dependent claims require additional distinguishing features that were not addressed by the Examiner in the Office Action. These additional features should certainly not be ignored, In re Boe et. Al., 184 USPQ 38 (CCPA 1974).

With respect to claims 17-24, Wong et al. does not disclose the use of a solubilizer. Examples of solubilzers are disclosed in the application at page 22, line 24 to page 25, line 5. The Examiner took the position that Wong et al. discloses "agents such as tartaric acid, mannitol, sucrose, and sodium chloride." Wong et al. lists these agents in the discussion regarding osmotic solutes (Col. 15, lines 10-16); however, there is no discussion regarding the use of solubilizers to increase the solubility of the drug. In addition, many of the listed osmotic solutes, such as mannitol, sucrose or sodium chloride, would not act to increase the solubility of a drug in aqueous solution.

With respect to claims 25-32, Wong et al. do not discuss including a fluidizing agent that causes the drug-containing composition to rapidly become fluid upon imbibing water. See application at page 20, line 14 to page 21, line 36. Wong et al. state that an optional osmagent may be included in the drug-containing composition; however, there is no discussion in Wong et al. regarding the need to select materials having high solubility to be the fluidizing agent, or that such materials should be present in a minimum amount to be effective.

With respect to claims 118-122, the drug in Wong et al. is not in the form of a solid amorphous dispersion. The examiner stated that Wong et al. disclose that the active may be "dispersed in suspending agents such as PVP", but there is no discussion regarding whether the drug is amorphous.

Claims 130-131 distinguish over Wong et al. by requiring a concentration-enhancing polymer in the drug-containing composition.

Claim 57 stands rejected over Wong et al. in view of Stevens et al in further view of the Jim Kling article. Kling was cited for its teaching of Viagra® as a drug for hypertension or erectile function. Wong and Stevens appear to have been cited for the reasons set forth by the Examiner in rejecting the remaining claims. Applicants note that claim 57 depends directly from claim 2. The rejection is traversed on the basis that the combination of Wong and Stevens is fatally defective for the reasons advanced above in Applicants discussion of claim 2 in relation to Wong and Stevens, and Applicants' comments relating to Wong and Stevens are incorporated herein by reference in this respect. The Kling article, beyond its disclosure of sildenafil citrate, does nothing otherwise to remedy the fatal defects of Wong and Stevens.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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Capsules

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. The soft gelatin capsule was invented by Mothes, a French pharmacist in 1833. During the following year DuBlanc obtained a patent for his soft gelatin capsules. In 1848 Murdock patented the two-piece hard gelatin capsule. Although development work has been done on the preparation of capsules from methylcellulose and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The gelatin used in the manufacture of capsules is obtained from collagenous material by hydrolysis. There are two types of gelatin, Type A, derived mainly from pork skins by acid processing, and Type B, obtained from bones and animal skins by alkaline processing. Blends are used to obtain gelatin solutions with the viscosity and bloom strength characteristics desirable for capsule manufacture.[50]

The encapsulation of medicinal agents remains a popular method for administering drugs. Capsules are tasteless, easily administered, and easily filled either extemporaneously or in large quantities commercially. In prescription practice the use of hard gelatin capsules permits a choice in prescribing a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility is an advantage over tablets. Some patients find it easier to swallow capsules than tablets, therefore preferring to take this form when possible. This preference has prompted pharmaceutical manufacturers to market the product in capsule form even though the product already has been produced in tablet form. While the industry prepares approximately 75% of its solid dosage forms as compressed tablets, 23% as hard gelatin capsules and 2% as soft elastic capsules, market surveys have indicated a consumer preference of 44.2% for soft elastic capsules, 39.6% for tablets and 19.4% for hard gelatin capsules.[51]

Hard Gelatin Capsules

The hard gelatin capsule, also referred to as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. The classic capsule shape is illustrated in Fig 39. These capsules are filled by introducing the powdered material into the longer end or body of the capsule and then slipping on the cap. Hard gelatin capsules are made largely from gelatin, FD&C colorants and sometimes an opacifying agent such as titanium dioxide; the USP permits the gelatin for this purpose to contain 0.15% sulfur dioxide to prevent decomposition during manufacture. Hard gelatin capsules contain 12 to 16% water, but the water content can vary depending on the storage conditions. When the humidity is low, the capsules become brittle; if stored at high humidities, the capsules become flaccid and lose their shape. Storage in high temperature areas also can affect the quality of hard gelatin capsules. Gelatin capsules do not protect hygroscopic materials from atmospheric water vapor as moisture can diffuse through the gelatin wall.

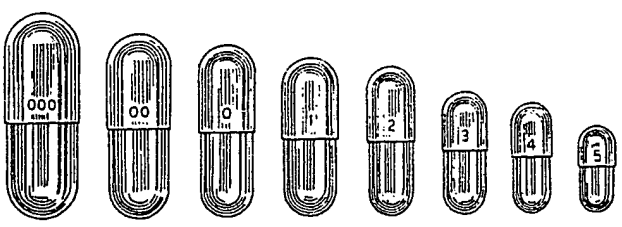


Fig 39. Hard gelatin capsules showing relatives sizes (courtesy, Parke-Davis).

Companies having equipment for preparing empty hard gelatin capsules include *Lilly*, *Parke-Davis*, *Scherer* and *SmithKline*. The latter's production is mainly for its own use; the others are suppliers to the industry. With this equipment stainless-steel pins, set in plates, are dipped into the gelatin solution, which must be maintained at a uniform temperature and an exact degree of fluidity. If the gelatin solution varies in viscosity, it correspondingly will decrease or increase the thickness of the capsule wall. This is important since a slight variation is sufficient to make either a loose or tight joint. When the pins have been withdrawn from the gelatin solution, they are rotated while being dried in kilns through which a strong blast of filtered air with controlled humidity is forced. Each capsule is stripped, trimmed to uniform length and joined, the entire process being mechanical. Capsule-making equipment is illustrated in Figs 40 and 41. These show the stainless-steel pins being dipped into the gelatin solutions and then being rotated through the drying kiln.

Capsules are supplied in a variety of sizes. The hard, empty capsules (Fig 39) are numbered from 000, the largest size which can be swallowed, to 5, which is the smallest. Larger sizes are available for use in veterinary medicine. The approximate capacity for capsules from 000 to 5 ranges from 600 to 30 mg, although this will vary because of the different densities of powdered drug materials.

Commercially filled capsules have the conventional oblong shape illustrated with the exception of capsule products of *Lilly* and *SmithKline*, which are of distinctive shape. For Lilly products, capsules are used in which the end of the body is tapered to give the capsule a bullet-like shape; products encapsulated in this form are called *Pulvules*. The *SmithKline* capsules differ in that both the ends of the cap and body are angular, rather than round.

After hard gelatin capsules are filled and the cap applied, there are a number of methods used to assure that the capsules will not come apart if subjected to vibration or rough handling, as in high-speed counting and packaging equipment. The capsules can be spot-welded by means of a heated metal pin pressed against the cap, fusing it to the body, or they may be banded with molten gelatin laid around the joint in a stripe and dried. Colored gelatin bands around capsules have been used for many years as a trademark by *Parke-Davis* for their line of capsule products, *Kapseals*. Another approach is used in the *Snap-Fit* and *Conti-Snap* capsules. A pair of matched locking rings are formed into the cap and body portions of the capsule. Prior to filling, these capsules are slightly longer than regular capsules of the same size.

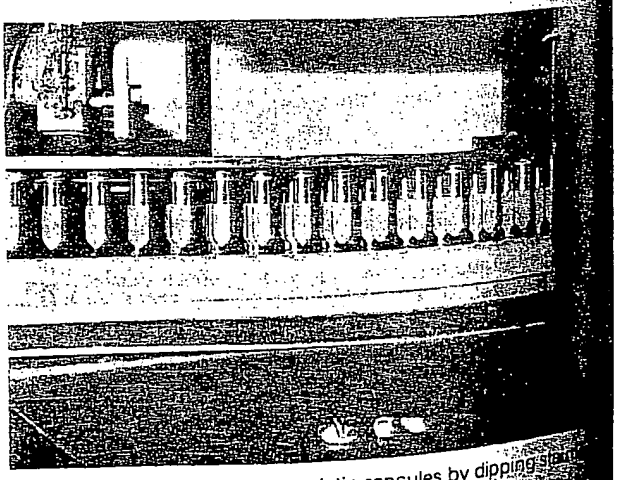
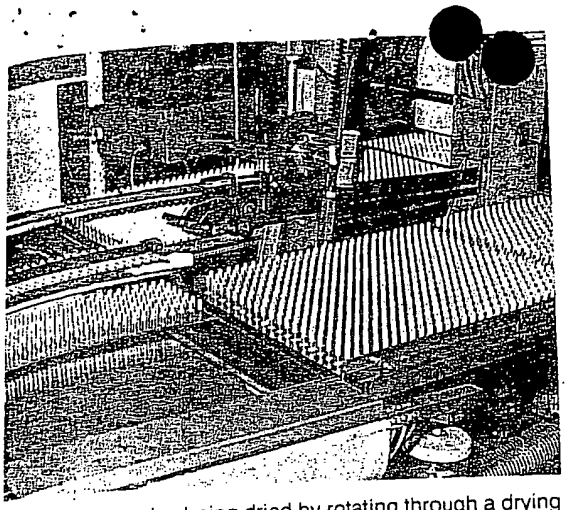


Fig 40. Manufacture of hard gelatin capsules by dipping steel pins into gelatin solutions (courtesy, Lilly).



Formed capsules being dried by rotating through a drying
urtesy, Lilly).

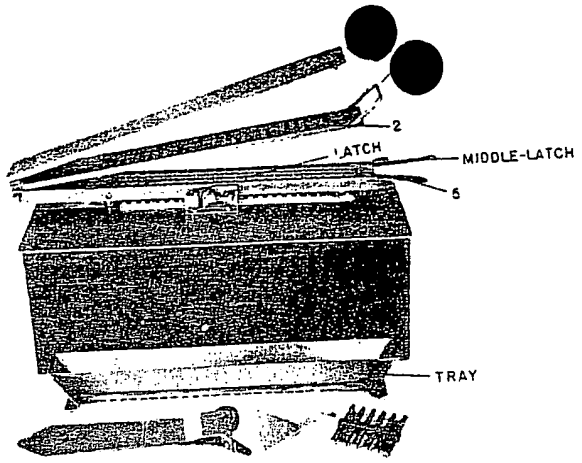


Fig 42. Hand-operated capsule machine (courtesy, Chemi-Pharm).

cking rings are engaged after filling, their length is ilent to that of the conventional capsule.
owing several tampering incidents, many pharmaceuti- mpanies now use any number of locking and sealing ologies in order safely to manufacture and distribute very useful dosage forms. Unfortunately, tamper- ant packaging has become standard for capsule prod-

s usually necessary for the pharmacist to determine the of the capsule needed for a given prescription through imentation. The experienced pharmacist, having calcu- the weight of material to be held by a single capsule, will select the correct size immediately. If the material wdered, the base of the capsule is filled and the top is ced. If the material in the capsule proves to be too y after weighing, a smaller size must be taken and the test ated. If the filled capsule is light, it is possible that more e forced into it by increasing the pressure or, if neces- some of the material may be placed in the cap. This is lesirable as it tends to decrease the accuracy of subdivi- and it is much better to select another size, the base of h will hold exactly the correct quantity. In prescription g it is wise to check the weight of each filled capsule.
addition to the transparent, colorless, hard gelatin cap- capsules are also available in various transparent colors as pink, green, reddish-brown, blue, yellow and black. ey are used, it is important to note the color as well as the sule size on the prescription so that in the case of renewal refilled prescription will duplicate the original. Colored sules have been used chiefly by manufacturers to give a cialty product a distinctive appearance. Titanium diox- is added to the gelatin to form white capsules, or to make opaque, colored capsule. In addition to color contrasts, ny commercial products in capsules are given further iden- cation by markings which may be the company's name, a bol on the outer shell of the capsule or by banding. Some nufacturers mark capsules with special numbers based on oded system to permit exact identification by the pharma- t or physician.

Extemporaneous Filling Methods

When filling capsules on prescription, the usual procedure o mix the ingredients by trituration, reducing them to a fine d uniform powder. The principles and methods for the iform distribution of an active medicinal agent in a powder ixture are discussed in Chapter 91. Granular powders do t pack readily in capsules and crystalline materials, espe- ally those which consist of a mass of filament-like crystals ich as the quinine salts, are not fitted easily into capsules unless powdered. Eutectic mixtures that tend to liquefy may be dispensed in capsules if a suitable absorbent such as magnesium carbonate is used. Potent drugs given in small doses usually are mixed with an inert diluent such as lactose before filling into capsules. When incompatible materials are prescribed together, it is sometimes possible to place one in a smaller capsule and then enclose it with the second drug in a larger capsule.

Usually, the powder is placed on paper and flattened with a spatula so that the layer of powder is not greater than about ¼ the length of the capsule which is being filled. This helps to keep both the hands and capsules clean. The cap is removed from the selected capsule and held in the left hand; the body is pressed repeatedly into the powder until it is filled. The cap is replaced and the capsule is weighed. In filling the capsule the spatula is helpful in pushing the last quantity of the material into the capsule. If each capsule has not been weighed, there is likely to be an excess or a shortage of material when the specified number of capsules have been packed. This condition is adjusted before dispensing the prescription.

A number of manual filling machines and automatic capsule machines are available for increasing the speed of the capsule-filling operation. Figure 42 illustrates a capsule-filling machine which was known formerly as the Sharp & Dohme machine. This equipment is now available through *ChemiPharm.* Many community pharmacists find this a useful piece of apparatus and some pharmaceutical manufacturers use it for small-scale production of specialty items. The machine fills 24 capsules at a time with the possible production of 2000 per day. Entire capsules are placed in the machine by hand; the lower plate carries a clamp which holds the capsule bases and makes it possible to remove and replace the caps mechanically. The plate holding the capsule bases is perforated for three sizes of capsules. The powder is packed in the bases; the degree of accuracy depends on the selection of capsule size and the amount of pressure applied in packing. The hand-operated machine (Model 300, *ChemiPharm*) illustrated in Fig 43 has a production capacity of 2000 capsules per hour. The machine is made for a single capsule size and cannot be changed over for other sizes. A different machine is required for any additional capsule size. Its principle of operation is similar to that of the Sharp & Dohme machine.

Machine Filling Methods

Large-scale filling equipment for capsules operates on the same principle as the manual machines described above, namely the filling of the base of the capsule. Compared with tablets, powders for filling into hard gelatin capsules require the minimum of formulation efforts. The powders usually contain diluents such as lactose, mannitol, calcium carbonate